PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 16 JUN 2005
WIPO PCT

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
29725P WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/003238	26.03.2004	28.03.2003

International Patent Classification (IPC) or national classification and IPC
A61L27/34, A61L27/56, C07K14/475

Applicant
BIOPHARM GESELLSCHAFT ZUR BIOTECHNOLOGISCHEN...

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.01.2005	17.06.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003238

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-34 as originally filed

   Sequence listings part of the description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-27 received on 27.01.2005 with letter of 26.01.2005

   Drawings, Sheets

   1/11-11/11 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following document (D1) cited in the International search report is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: US 6,118,043 A (Nies B. et al.)

Novelty

Document D1 discloses (cf. claims 1, 7-13, 19) a bone replacement material comprising a porous matrix and fibroblast growth factor (FGF) adsorbed thereon. The material is prepared by impregnating the porous matrix with a solution of FGF followed by drying. The subject-matter of claims 1-27 of the present application differs from the disclosure of D1 by the choice of pH and ionic concentration of the morphogenetic protein solution and is therefore novel according to Article 33(2) PCT.

Inventive Step

Document D1, which is considered to represent the most relevant prior art, discloses (claims 1, 7-13, 19) the impregnation of porous implants with a solution of 50 µg FGF to provide a bone replacement material having a biological activity as close as possible to that of endogenous bone transplantation.

In view of D1, the objective technical problem underlying the present application can be formulated as to provide osteoinductive matrix materials for use in the pharmaceutical field which are homogeneously coated with morphogenetic proteins.

The solution proposed in the present application is a porous osteoinductive material comprising a matrix material having morphogenetic protein(s) adsorbed on inner or outer surfaces thereon, which can be obtained by selecting a pH and an ionic concentration of the solution that avoid precipitation of the morphogenetic proteins.

Since the relation between the pH and low ionic concentration of the morphogenetic protein solution on the one hand and the solubility of the morphogenetic proteins on the

other hand is unexpected and allows to obtain a more homogeneous coating of the matrix material, the subject-matter of claims 1-25 is based on an inventive activity according to Article 33(3) PCT.

Claims

1. Osteoinductive material comprising a matrix material and, adsorbed on inner and/or outer surfaces of this matrix material, morphogenetic protein(s), wherein said osteoinductive material is obtainable by contacting the matrix material and the morphogenetic protein(s) under suitable conditions to keep the protein stable and dissolved in a solution, thereby allowing that the matrix material becomes evenly coated with the morphogenetic protein(s), wherein said suitable conditions are selected from

   (a) using a buffer or solvent which is capable of maintaining a pH below 4.5 or above 10.3 during the coating procedure, or

   (b) using a buffer or solvent which has an ionic concentration of 100 mmol/l or less and is capable of maintaining a pH below 5.2 or above 9.5 during the coating procedure.

2. Osteoinductive material according to claim 1, wherein the morphogenetic protein contains at least a 7 cysteine region characteristic for TGF-ß superfamily proteins.

3. Osteoinductive material according to claim 1 or 2, wherein the morphogenetic protein is a mature protein or a biologically active part or variant thereof.

4. Osteoinductive material according to any one of claims 1 to 3, wherein the morphogenetic protein belongs to the TGF-ß-, BMP-, GDF-, activin- or GDNF-family.

5. Osteoinductive material according to any one of claims 1 to 4, wherein the morphogenetic protein is a dimeric protein.

6. Osteoinductive material according to any one of claims 1 to 5, wherein the morphogenetic protein is BMP2, BMP7, BMP12, BMP13, MP52 (GDF5) or a biologically active part or variant thereof.

7. Osteoinductive material according to any one of claims 1 to 4, wherein the morphogenetic protein is a protein lacking the cysteine residue which is responsible for dimer formation in the respective naturally occurring proteins.

8. Osteoinductive material according to any one of claims 1 to 4 and 7, wherein the morphogenetic protein contains a consensus sequence according to

Formula I: $C(Y)_{25-29}CYYYC(Y)_{25-35}XC(Y)_{27-34}CYC$ or

Formula II: $C(Y)_{28}CYYYC(Y)_{30-32}XC(Y)_{31}CYC$,

wherein C denotes cysteine, Y denotes any amino acid and X denotes any amino acid except cysteine.

9. Osteoinductive material according to any one of claims 1 to 4, 7 and 8, wherein the protein is a monomeric form of MP52.

10. Osteoinductive material according to claim 9, wherein the protein is MP52-Ala83 or a biologically active part or variant thereof.

11. Osteoinductive material according to any one of the preceding claims, wherein the matrix material is a biocompatible material.

12. Osteoinductive material according to any one of the preceding claims, wherein the matrix material is a natural material, a modified natural material or a synthetic material.

13. Osteoinductive material according to any one of the preceding claims, wherein the matrix material is a porous material.

14. Osteoinductive material according to any one of the preceding claims, wherein the matrix material comprises at least one of the following substances: a) collagen, b) $Ca(OH)_2$, c) polylactide or polylactide derivatives, d) hyaluronic acid, e) polyoxyethylene polyoxypropylene copolymers f) calcium phosphate, g) a combination of hydroxy apatite and collagen h) a combination of polyglycolic acid and polylactic acid or polylactid derivatives.

15. Osteoinductive material according to any one of the preceding claims, wherein the buffer or solvent used for coating has an ionic concentration of 80 mmol/l or less, 40 mmol/l or less, 20 mmol/l or less, 10 mmol/l or less, or 5 mmol/l.

16. Osteoinductive material according to any one of the preceding claims, wherein the buffer or solvent used for coating further comprises saccharides.

17. Osteoinductive material according to any one of the preceding claims, wherein the buffer or solvent used for coating further comprises alcohols or other organic solvents.

18. Osteoinductive material according to anyone of the preceding claims, wherein the buffer or solvent used for coating further comprises soaps or syndets.

19. Osteoinductive material according to any of the preceding claims, wherein the morphogenetic protein(s) is covalently or noncovalently linked to polyethylene glycols.

20. Osteoinductive material according to any one of the preceding claims, wherein the buffer or solvent used for acidic coating contains HCl or sodium acetate.

21. Osteoinductive material according to any one of the preceding claims, wherein the buffer or solvent used for basic coating contains NaOH or sodium carbonate/sodium bicarbonate.

22. Process for the production of an osteoinductive material according to claims 1 to 20, said process comprising contacting a matrix material with a solution of at least one morphogenetic protein characterized in that substances contained in said solution are selected to enable adjustment of the pH of the solution to below 5.2 even when in contact with the matrix material.

23. Process for the production of an osteoinductive material according to claims 1 to 19 and 21, said process comprising contacting a matrix material with a solution of a morphogenetic protein characterized in that substances contained in said solution are selected to enable adjustment of the pH of the solution to above 9.5 even when in contact with the matrix material.

24. Use of an osteoinductive material according to claims 1 to 21 for the preparation of a medicament for use in indications in which monomeric or dimeric morphogenetic proteins have been proven to be useful.

25. Use according to claim 24, wherein the osteoinductive material is used for preventing, alleviating or treating symptoms or conditions of diseases or abnormal conditions of cartilage, bone, connective tissue including tendon and/or ligament, periodontal or dental tissue, neural tissue, tissue of the sensory system, liver, pancreas, cardiac, blood vessels, renal, uterine and thyroid tissue, skin, mucous membranes, endothelium, epithelium.

26. Use according to claim 24 or 25, for promotion or induction of nerve growth, tissue repair and regeneration, angiogenesis, wound healing including ulcers, burns, injuries or skin grafts, induction of proliferation of progenitor cells or bone marrow cells, for regeneration of functional attachment between connective tissue and bone, cartilage repair, treatment of osteoporosis or osteoarthritis, to correct non-union fractures, acquired or congenital craniofacial, skeletal or dental abnormalities, for non-skeletal tissue replacement in plastic or reconstructive surgery.

27. Use according to any one of claims 24-26, wherein the disease or abnormal condition is caused by ischemic or traumatic injury, degenerative disease, cardiomyopathies, atherothrombotic or cardioembolic strokes, ulceration, cirrhosis, emphysema, cell senescence or quiescence.